GAU 1656

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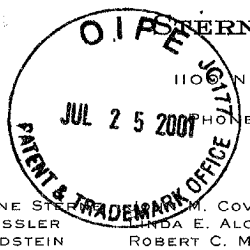

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July 25, 2001

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Commissioner for Patents
Washington, D.C. 20231

Art Unit 1656

Re: U.S. Utility Patent Application
Appl. No. 09/666,890; Filed: September 20, 2000
For: **Nucleic Acid Marker Ladder for Estimating Mass**
Inventor: James L. Hartley
Our Ref: 0942.2570003/RWE/AGL

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Fee Transmittal (PTO/SB/17) *(in duplicate)*;
2. Reply Under 37 C.F.R. §1.111;
3. Terminal Disclaimer Over a Prior Patent (PTO/SB/26);
4. Certificate Under 37 C.F.R. §3.73(b) w/a copy of an Assignment to Life Technologies, Inc. (1 page) and a copy of the Merger Document between Life Technologies, Inc. and Invitrogen Corporation (3 pages);
5. One (1) return postcard; and
6. Our check no. **32022** for **$110.00** to cover the Terminal Disclaimer fee.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036. A duplicate copy of this letter is enclosed.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond
Attorney for Applicant
Registration No. 32,893

RWE/AGL:kim
Enclosures

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SKGF Rev. 4/27/00 mac

PTO/SB/17 (11-00)
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FEE TRANSMITTAL for FY 2001

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT ($) 110.00

Complete if Known	
Application Number	09/666,890
Filing Date	September 20, 2000
First Named Inventor	James L. HARTLEY
Examiner Name	Houtteman, S.
Group Art Unit	1656
Attorney Docket No.	0942.2570003/RWE

METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayment to:

Deposit Account Number: 19-0036

Deposit Account Name: Sterne, Kessler, Goldstein & Fox P.L.L.C.

☐ Charge Any Additional Fee Required Under 37 CFR §§ 1.16 and 1.17

☐ Applicant claims small entity status See 37 CFR 1.27

2. ☒ Payment Enclosed: Check No. 32022

☒ Check ☐ Credit card ☐ Money Order ☒ Other*

*Charge any deficiencies or credit any overpayments in the fees or fee calculations of Parts 1, 2 and 3 below to Deposit Account No. 19-0036.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
101	710	201	355	Utility filing fee	
106	320	206	160	Design filing fee	
107	490	207	245	Plant filing fee	
108	710	208	355	Reissue filing fee	
114	150	214	75	Provisional filing fee	

SUBTOTAL (1) ($) -0-

2. EXTRA CLAIM FEES

	Extra	Fee from below	Fee Paid
Total Claims ____ - 20** =	____	X ____	= ____
Indep. Claims ____ - 3** =	____	X ____	= ____
Multiple Dependent		____	= ____

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
103	18	203	9	Claims in excess of 20
102	80	202	40	Independent claims in excess of 3
104	270	204	135	Multiple dependent claim
108	80	209	40	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) -0-

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for *ex parte* reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	390	216	195	Extension for reply within second month	
117	890	217	445	Extension for reply within third month	
118	1,390	218	695	Extension for reply within fourth month	
128	1,890	228	945	Extension for reply within fifth month	
119	310	219	155	Notice of Appeal	
120	310	220	155	Filing a brief in support of an appeal	
121	270	221	135	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,240	241	620	Petition to revive - unintentional	
142	1,240	242	620	Utility issue fee (or reissue)	
143	440	243	220	Design issue fee	
144	600	244	300	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	130	123	130	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	481	40	Recording each patent assignment per property (times number of properties)	
146	710	246	355	Filing a submission after final rejection (37 CFR 1.129(a))	
149	710	249	355	For each additional invention to be examined (37 CFR 1.129(b))	
179	710	279	355	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	
Other fee (specify) :				Terminal Disclaimer	$110.00
Other fee (specify) :					

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 110.00

SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	Robert W. Esmond	Registration No. (Attorney/Agent)	32,893	Telephone	202-371-2600
Signature	Robert W. Esmond			Date	July 25, 2001

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
James HARTLEY
Appl. No. 09/666,890
Filed: September 20, 2000
For: **Nucleic Acid Marker Ladder for Estimating Mass**

Art Unit: 1656
Examiner: S. Houtteman
Atty. Docket: 0942.2570003/RWE/AGL

#7
7/30/01

Reply Under 37 C.F.R. § 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Office Action dated April 25, 2001 (PTO Prosecution File Wrapper Paper No. 6), Applicant submits the following Remarks.

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Remarks

Reconsideration and withdrawal of the outstanding rejections are respectfully requested. Claims 15-33 are now pending in this application with claims 15, 23 and 31 being the independent claims. Reconsideration of claims 15-33 is respectfully requested.

I. The Rejection under Obviousness-Type Double Patenting over the '201 Patent

Claims 15-33 have been rejected by the Examiner under the doctrine of obviousness-type double patenting over the claims of U.S. Patent No. 5,834,201 ("the '201 patent"). Applicant respectfully traverses this rejection. Enclosed herewith is a Terminal Disclaimer to Obviate a Double Patenting Rejection Over a Prior Patent and Certificate Under 37 C.F.R. § 3.73(b).

In view of the terminal disclaimer and Certification, Applicant submits that the rejection is now moot. Withdrawal of the rejection is respectfully requested.

II. The Rejection under 35 U.S.C. § 103(a) Over Carlson in view of Hartley, Mullis and Maniatis

Claims 15-33 have been rejected by the Examiner under 35 U.S.C. § 103(a) as allegedly obvious over Carlson *et al.*, European Patent Application No. 0 466 404 ("Carlson") in view of Hartley *et al.*, *Gene 13*:347-353 (1981) ("Hartley"), Mullis *et al.*, U.S. Patent No. 4,683,195 ("Mullis") and Maniatis *et al.*, MOLECULAR CLONING: A LABORATORY MANUAL, 468-469 (1982) ("Maniatis"). Applicant respectfully traverses this rejection.

There is no motivation in the prior art to combine the references in the manner proposed by the Examiner. Rather, it is only by using the claims of the subject application as a template that the Examiner has sifted through the various references in the prior art and cited certain portions thereof in an attempt to reconstruct the claimed invention.

For example, the Examiner has alleged that "Hartley et al. teaches this ladder wherein the integer is 123. Hartley states 'it should be possible to polymerize any DNA

segment by this method'." Such an allegation, however, incorrectly characterizes the teachings of Hartley.

Contrary to the Examiner's allegation, Hartley does not relate to DNA marker ladders, *i.e.*, mixtures of DNA fragments for use as calibration standards in gel electrophoresis. Rather, Hartley is directed to a "method for the insertion of multiple copies of a DNA segment into a plasmid and subsequent cloning of the plasmid . . . ." The potential uses of this method are disclosed as including "production of large amounts of small, homogeneous DNAs for physical studies such as X-ray crystallography, and increasing the expression of cloned genes in bacteria." Thus, Hartley is not even remotely relevant to the presently claimed invention.

More specifically, a reference is reasonably pertinent to the problem being solved if, and only if, "it is one which, because of the [subject] matter with which it deals, [would] logically have commended itself to an inventor's attention in considering his problem." *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1061 (Fed. Cir. 1992). The Hartley reference cited by the Examiner does not satisfy this standard.

In the present case, the present Applicant was seeking a DNA marker ladder that could be used as a reference standard for determining both the size of an unknown DNA molecule and the amount thereof in a sample. The Hartley reference, however, was seeking a method for insertion of multiple copies of a particular DNA segment, such as a gene, into a plasmid to increase subsequent expression of that DNA segment in a host organism. One of ordinary skill in the art preparing a marker ladder capable of calibrating both the size and amount of DNA in a sample simply would not look to a

reference that relates to polymerizing a particular gene for insertion into an expression vector.

Similarly, there is no motivation to combine Maniatis with the other references in the manner proposed by the Examiner. Indeed, for at least the following two reasons, one skilled in the art would not have been motivated to combine Maniatis with Carlson.

First, Maniatis expressly teaches that "[t]he standard DNA solution [in a gel electrophoresis assay for determining the quantity of DNA in a sample] should contain a *single* species of DNA, approximately the same size as the unknown DNA." The use of a single strand of DNA as the reference standard is critical to the method disclosed by Maniatis because that method requires the concentration of DNA in a given lane in the assay to be known (so that the concentration of the amount DNA can be determined by direct comparison of the relative intensity of their respective fluorescence).

In striking contrast to Maniatis, however, Carlson employs DNA marker ladders in a gel electrophoresis assay to determine the size of an unknown DNA molecule, *i.e.*, the size of the unknown DNA is calculated by comparing the distance it migrates to the distances migrated by DNA molecules of known size. As described both in Carlson and the above-identified application, such DNA marker ladders are composed of a *mixture* of many DNA fragments of varying size. A mixture of DNA fragments is important so that the unknown DNA can be compared to a number of DNA fragments of differing size -- the more fragments available for comparison, the more accurate the resulting estimate of size is likely to be. Indeed, Carlson strongly suggests a preference for high numbers of DNA fragments in any given ladder, stating that "[t]he number of [DNA fragments] pooled is at least 5, preferably at least 10, more preferably at least 15, yet more preferably

at least 20, and most preferably at least 25." Moreover, Carlson does disclose a marker ladder comprising an endonuclease digest, Carlson, however, does not teach that the relative concentrations of the fragments can be controlled during digestion to produce a marker ladder capable of quantifying the amount of DNA present in a sample, like the presently claimed marker ladder.

Secondly, Maniatis specifically teaches staining with ethidium bromide for visualizing the reference DNA and the sample DNA and thereby determining by comparison the amount of DNA in the sample. Conversely, however, Carlson expressly teaches that ethidium bromide staining should *not* be used as a method of visualization when using an endonuclease digest marker ladder because "the ladder DNA may appear as a "smear" due to the multitude of fragments." Such smearing is strongly disfavored as it makes comparison of the unknown DNA with the reference DNA very difficult and prone to error.

The respective teachings above are so divergent, indeed, even to the point of teaching away from one another, that there is no motivation to combine these references as proposed by the Examiner. One skilled in the art, possessing either Maniatis or Carlson, would plainly not look to the other in seeking to modify one simply because the teachings thereof directly contradict the teachings in the first (the ordinary artisan, however, is one who thinks along the lines of conventional wisdom in the art, not one who seeks to innovate or experiment; *see Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 USPQ 293 (Fed. Cir. 1985)).

In light of their contradictions and inconsistencies, anyone trying to combine Maniatis with Carlson would clearly be working *outside* the lines of conventional

wisdom in the art. It is wholly improper to combine two references when the references themselves teach away from that combination, as do Maniatis and Carlson, and such a combination is not obvious. *In re Graselli*, 713 F.2d 731, 218 USPQ 769 (Fed. Cir. 1983).

With respect to the citation of Mullis, simply because a technique is available to one of ordinary skill in the art to place restriction sites in a nucleic acid molecule, this does not render obvious the presently claimed marker ladder or even a nucleic acid molecule having internal restriction sites (such as the one from which the claimed marker ladder is generated). To the contrary, there must still be some suggestion in the prior art that suggests the compound in order to make out a *prima facie* case. *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210 (Fed. Cir. 1995). A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be performed. *Id.* at 1554, 34 USPQ2d at 1216.

In view of the above discussion of the references, it is clear that hindsight is required to interpret the cited references and select certain teachings thereof in an attempt to reconstruct the presently claimed invention. Such hindsight, however, is no substitute for the requisite motivation necessary to sustain a rejection for obviousness under § 103.

The final requirement of every *prima facie* case of obviousness is that the combined references must teach *every limitation* of the claims. MANUAL OF PATENT EXAMINING PROCEDURE § 2143.03 (Rev. 1, February 2000); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990)("[f]ocusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness").

In the present case, however, even if the teachings of the references cited by the Examiner were combined, that combination does not teach or suggest each and every limitation of the various claimed embodiments of the present invention.

In addition to the factors required to establish a *prima facie* case of obviousness, a conclusion of obviousness *vel non* is based on a totality of the evidence. Accordingly, before obviousness can be found, secondary considerations which may not be immediately apparent from the express language of the claims, such as the particular advantages of the claimed invention, must be evaluated. *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). These secondary considerations must be considered as a whole along with the initial facts on which the Examiner's *prima facie* case was based, *i.e.*, the secondary considerations should not be regarded as a rebuttal of the Examiner's position, but rather a final determination of obviousness must be made considering the entire record. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir.1990).

Of particular importance are the unique advantages of the inventive marker ladder. It must be remembered that

> [w]hen prior art references require selective combination by a court to render obvious a subsequent invention, there must be some reason for the combination other than hindsight gleaned from the invention itself. There must be "something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination."
>
> *Critical to the analysis is an understanding of the particular results achieved by the new combination.*

Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143, 227 USPQ 543, 551 (Fed. Cir. 1985)(citations omitted; emphasis supplied).

As described in the specification of the present application, the inventive marker ladder is useful as a calibration standard in electrophoresis. *Specification*, page 9, lines 9-10. Because the sizes of the various fragments that make up the inventive ladder are multiples of an integer, the presently claimed invention is extremely convenient and easy to use and so allows the ordinary artisan to quickly calculate the size of an unknown nucleic acid fragment. *Id.* at lines 10-13. The presently claimed marker ladder, however, *also* allows the ordinary artisan to determine the mass of the unknown nucleic acid, *i.e.*, how much of the unknown nucleic acid is present in the sample being tested. *Id.* at lines 14-16.

This latter feature is possible because all of the fragments that compose the inventive marker ladder are generated from a *single* nucleic acid molecule, the resultant fragments are present in known proportions to one another. *Id.* at lines 17-21. If a skilled artisan made the fragments separately and then mixed those fragments to form a marker ladder, that worker would need to measure the concentration of each fragment as well as the volume of that fragment added to the ladder mixture. All of these concentration and volume measurements represent a substantial increase in the labor necessary to prepare a nucleic acid marker ladder as well as providing significant additional opportunities for the introduction of errors. Such systematic errors are *absent* when using the inventive marker ladder.

This advantageous combination of measurements, *i.e.*, measurement of both the size of an unknown nucleic acid fragment and the concentration of that unknown

fragment in a mixture, that can be obtained in a *single* experiment using the inventive marker ladder is not suggested by or apparent from the Examiner's combination of references. An evaluation of the obviousness of a claimed combination requires consideration of the results achieved with that combination. *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 16 USPQ2d 1923 (Fed. Cir. 1990). Thus, even if, *arguendo*, a *prima facie* case of obviousness has been established, the discovery that the inventive marker ladder enables a single assay to determine both the size and concentration of unknown DNA in a sample, without the systematic errors associated with prior art assays, plainly refutes any such *prima facie* case.

Claims 15-33 are in condition for immediate allowance. An early indication of allowance is therefore respectfully solicited.

III. Conclusion

All of the stated grounds of rejections have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding objections and rejections. Applicant believes that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. Prompt and favorable consideration of this Amendment is respectfully requested.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Robert W. Esmond

Robert W. Esmond
Attorney for Applicant
Registration No. 32,893

Date: July 25, 2001

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